Skeletogenic phenotype of human Marfan embryonic stem cells faithfully phenocopied by patient-specific induced-pluripotent stem cells.

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Public Summary:
Marfan syndrome (MFS) is an inherited connective-tissue disorder that occurs in one in 10,000 to one in 20,000 individuals caused by mutations in the gene encoding Fibrillin-1 (FBN1) a large molecule component of extracellular matrix. Individual affected by MFS show several clinical features of skeletal, cardiovascular and ocular (eye) system. The clinical features of skeletal system are increased height, disproportionately long bones and digits, joint laxity and vertebral column deformity (scoliosis). Moreover, people with this syndrome suffer from osteopenia, or poor bone mineralization. Aortic (large blood vessel) root dilatation, aortic regurgitation, heart mitral valve prolapsed and heart mitral regurgitation are the cardiovascular features. Eye defects such as myopia, corneal flatness and subluxation of the lenses (ectopia lentis) are present in MFS patients. We have established human embryonic stem cells from a MFS embryo and human induced pluripotent stem cells (iPS) derived from the skin of Marfan patients. Analysis of these cell lines have unveiled unique features showing impaired ability to form bone, and all too readily formed cartilage. These aberrations mirror the most prominent clinical skeletal manifestation of the disease. Moreover, our research revealed that an alteration of Transforming Growth Factor ↑ (TGF↑ signaling is responsible for the pathological conditions observed. Importantly, this study demonstrated for the first time the faithful alignment of pathological features in cells obtained from both human embryonic stem cells and iPS cells providing complementary and powerful tools to gain further insights into human molecular pathogenesis, especially of MFS.

Scientific Abstract:
Marfan syndrome (MFS) is a heritable connective tissue disorder caused by mutations in the gene coding for FIBRILLIN-1 (FBN1), an extracellular matrix protein. MFS is inherited as an autosomal dominant trait and displays major manifestations in the ocular, skeletal, and cardiovascular systems. Here we report molecular and phenotypic profiles of skeletogenesis in tissues differentiated from human embryonic stem cells and induced pluripotent stem cells that carry a heritable mutation in FBN1. We demonstrate that, as a biological consequence of the activation of TGF-beta signaling, osteogenic differentiation of embryonic stem cells with a FBN1 mutation is inhibited; osteogenesis is rescued by inhibition of TGF-beta signaling. In contrast, chondrogenesis is not perturbated and occurs in a TGF-beta cell-autonomous fashion. Importantly, skeletal phenotypes observed in human embryonic stem cells carrying the monogenic FBN1 mutation (MFS cells) are faithfully phenocopied by cells differentiated from induced pluripotent-stem cells derived independently from MFS patient fibroblasts. Results indicate a unique phenotype uncovered by examination of mutant pluripotent stem cells and further demonstrate the faithful alignment of phenotypes in differentiated cells obtained from both human embryonic stem cells and induced pluripotent-stem cells, providing complementary and powerful tools to gain further insights into human molecular pathogenesis, especially of MFS.

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